PA 1297240

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

March 21, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: ***60/519,690***
FILING DATE: ***November 13, 2003***

GB/04/50026

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

P. SWAIN
Certifying Officer

SUBSTITUTE PTO/SB/16 (5-03)

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR §1.53(c).

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Mary Ellen	Rybak	Princeton, NJ

Additional Inventors are being named on the 0 separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

COMBINATION

CORRESPONDENCE ADDRESS

Direct all correspondence to:

[X] Customer Number: 26161

OR

[ ] Firm *or* Individual Name					
Address					
Address					
City		State		ZIP	
Country	United States	Telephone		Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

[X] Specification	*Number of Pages* 15	[] CD(s), Number	
[] Drawing(s)	*Number of Sheets*	[] Other (specify)	
[] Application Data Sheet. See 37 CFR 1.76.			

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

[] Applicant Claims small entity status. See 37 CFR 1.27.

[X] A check or money order is enclosed to cover the filing fees.

[] The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 06-1050

[] Payment by credit card. Form PTO-2038 is attached.

FILING FEE AMOUNT ($): $160

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

[X] No.

[] Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

Signature _____ Date November 13, 2003

Typed Name Louis Myers, Reg. No. 35,965

Telephone No. (617) 542-5070

Docket No. 14620-028P01

20755036.doc

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EL 228 030 688 US

Date of Deposit November 13, 2003

Attorney's Docket No.: 14620-028P01

PROVISIONAL APPLICATION FOR PATENT

under

37 CFR §1.53(c)

TITLE: COMBINATION

APPLICANT: MARY ELLEN RYBAK

CERTIFICATE OF MAILING BY EXPRESS MAIL

Express Mail Label No. EL 228 030 688 US

November 13, 2003

Date of Deposit

Combination

The invention relates to a combination of medicaments, more particularly a combination of medicaments for use in the treatment of cancer.

FIELD OF THE INVENTION

The present invention is directed to the use of ecteinascidin 743 and more especially combination products containing this compound for cancer therapy, in particular to the use of ecteinascidin 743 in combination with another active drug for the treatment of cancer.

BACKGROUND OF THE INVENTION

Cancer comprises a group of malignant neoplasms that can be divided into two categories, carcinoma, comprising a majority of the cases observed in the clinics, and other less frequent cancers, which include leukemia, lymphoma, central nervous system tumors and sarcoma. Carcinomas have their origin in epithelial tissues while sarcomas develop from connective tissues and those structures that had their origin in mesoderm tissues. Sarcomas can affect, for instance, muscle or bone and occur in the bones, bladder, kidneys, liver, lung, parotid, spleen, etc.

Cancer is invasive and tends to metastasise to new sites. It spreads directly into surrounding tissues and also may be disseminated through the lymphatic and circulatory systems.

Many treatments are available for cancer, including surgery and radiation for localised disease, and drugs. However, the efficacy of available treatments on many cancer types is limited, and new, improved forms of treatment showing clinical benefit are needed.

This is especially true for those patients presenting with advanced and/or metastatic disease. It is also true for patients relapsing with progressive disease after having been previously treated with established therapies for which further treatment with the same therapy is mostly ineffective due to acquisition of resistance or to limitations in administration of the therapies due to associated toxicities.

Chemotherapy plays a significant part in cancer treatment, as it is required for treatment of advanced cancers with distant metastasis and often helpful for tumor reduction before surgery, and many anti-cancer drugs have been developed based on various modes of action.

The most commonly used types of anticancer agents include: DNA-alkylating agents (for example, cyclophosphamide, ifosfamide), antimetabolites (for example, methotrexate, a folate antagonist, and 5-fluorouracil, a pyrimidine antagonist), microtubule disrupters (for example, vincristine, vinblastine, paclitaxel), DNA intercalators (for example, doxorubicin, daunomycin, cisplatin), and hormone therapy (for example, tamoxifen, flutamide). The ideal antineoplastic drug would kill cancer cells selectively, with a wide therapeutic index relative to its toxicity towards non-malignant cells. It would also retain its efficacy against malignant cells, even after prolonged exposure to the drug. Unfortunately, none of the current chemotherapies possess an ideal profile. Most possess very narrow therapeutic indexes and, in practically every instance, cancerous cells exposed to slightly sublethal concentrations of a

chemotherapeutic agent will develop resistance to such an agent, and quite often cross-resistance to several other antineoplastic agents.

The ecteinascidins (herein abbreviated ETs) are exceedingly potent antitumor agents isolated from the marine tunicate *Ecteinascidia turbinata.* Several ecteinascidins have been reported previously in the patent and scientific literature. See, for example U.S. Pat. No. 5,089,273, which describes novel compositions of matter extracted from the tropical marine invertebrate, *Ecteinascidia turbinata*, and designated therein as ecteinascidins 729, 743, 745, 759A, 759B and 770. These compounds are useful as antibacterial and/or antitumor agents in mammals. U.S. Pat. No. 5,478,932 describes ecteinascidins isolated from the Caribbean tunicate *Ecteinascidia turbinata*, which provide *in vivo* protection against P388 lymphoma, B16 melanoma, M5076 ovarian sarcoma, Lewis lung carcinoma, and the LX-1 human lung and MX-1 human mammary carcinoma xenografts.

One of the ETs, ecteinascidin-743 (ET-743), is a novel tetrahydroisoquinoline alkaloid with considerable antitumor activity in murine and human tumors *in vitro* and *in vivo*, and is presently in clinical trials. ET-743 possesses potent antineoplastic activity against a variety of human tumor xenografts grown in athymic mice, including melanoma and ovarian and breast carcinoma.

A clinical development program of ET-743 in cancer patients was started with phase I studies investigating 1-hour, 3-hour, 24-hour and 72-hour intravenous infusion schedules and a 1 hour daily x 5 (dx5) schedule. Promising responses were observed in patients with sarcoma and breast and ovarian carcinoma. Therefore this new drug is currently under intense investigation in several phase II clinical trials in cancer patients with a variety of neoplastic diseases. Further detail on the use of ET-743

for the treatment of the human body for cancer is given in WO 0069441, incorporated herein by reference in its entirety.

A recent review of ET-743, its chemistry, mechanism of action and preclinical and clinical development can be found in Kesteren, Ch. Van et al., **2003**, *Anti-Cancer Drugs*, 14 (7), pages 487-502: "ET-743 (trabectedin, ET-743): the development of an anticancer agent of marine origin", and references therein.

Combination therapy using drugs with different mechanisms of action is an accepted method of treatment which helps prevent development of resistance by the treated tumor. *In vitro* activity of ET-743 in combination with other anticancer agents has been studied, see for example WO 02 36135, incorporated herein by reference in its entirety.

It is an object of the invention to provide an efficacious combination product for treatment of cancer. More particularly, an object of this invention is an effective cancer combination therapy.

SUMMARY OF THE INVENTION

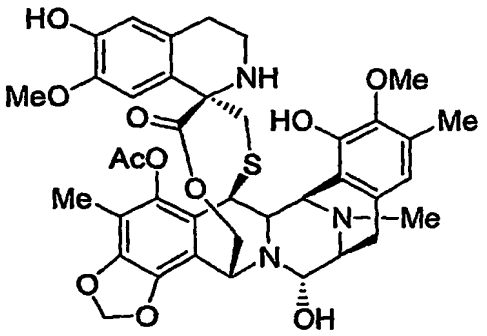
According to the present invention, we provide a combination therapy for the treatment of cancer which employs ecteinascidin 743 and 5-fluorouracil. Typical dosing protocols for the combination therapy are provided, where the 5-fluorouracil is given in the form of a pro-drug, especially an oral pro-drug exemplified by capecitabine (Xeloda®). From phase I clinical trials, we have determined that a combination of ET-743 and capecitabine is tolerable and feasible, with evidence of antitumor activity.

We also provide a method of treating a cancer patient, which comprises administering ET-743 and a pro-drug of 5-fluorouracil, notably capecitabine. The ET-743 and pro-drug of 5-fluorouracil are preferably administered sequentially, with multiple oral administrations of the pro-drug of 5-fluorouracil following infusion of ET-743.

We further provide the use of ET-743 in the preparation of a medicament for carrying out the method of treatment. We also provide the use of the pro-drug of 5-fluorouracil, notably capecitabine, in the preparation of a medicament for carrying out the method of treatment. We provide the use of ET-743 and the pro-drug of 5-fluorouracil, notably capecitabine, in the preparation of a medicament for carrying out the method of treatment.

DETAILED DESCRIPTION

ET-743 is a natural compound represented by the following formula:



As used herein, the term "ET-743" also covers any pharmaceutically acceptable salt, ester, solvate, hydrate or a prodrug compound which, upon administration to the recipient is capable of providing (directly or

indirectly) the compound ET-743. The preparation of salts and other derivatives, and prodrugs, can be carried out by methods known in the art.

ET-743 is typically supplied and stored as a sterile lyophilized product, with ET-743 and excipient in a formulation adequate for therapeutic use, in particular a formulation containing mannitol and a phosphate salt buffered to an adequate pH.

It is currently preferred to administer the ET-743 by infusion. The infusing step is typically repeated on a cyclic basis, which may be repeated as appropriate over for instance 1 to 20 cycles. The cycle includes a phase of infusing ET-743, and usually also a phase of not infusing ET-743. Typically the cycle is worked out in weeks, and thus the cycle normally comprises one or more weeks of an ET-743 infusion phase, and one or more weeks to complete the cycle. In one embodiment a cycle of 3 weeks is preferred, alternatively it can be from 2 to 6 weeks. The infusion phase can itself be a single administration in each cycle of say 1 to 72 hours, more usually of about 1, 3 or 24 hours, or infusion on a daily basis in the infusion phase of the cycle for preferably 1 to 5 hours, especially 1 or 3 hours. Thus, for example, the ET-743 might be administered on each of the first five days of a 3 week cycle. We currently prefer a single administration at the start of each cycle. Preferably the infusion time is about 1, 3 or 24 hour. In one embodiment an infusion time of about 3 hours is preferred.

The dose will be selected according to the dosing schedule, having regard to the existing data on Dose Limiting Toxicity, on which see for example the incorporated WO patent specifications, and also see Kesteren, Ch. Van *et al.*, 2003, Anti-Cancer Drugs, 14 (7), pages 487-502: "ET-743 (trabectedin, ET-743): The development of an anticancer agent of marine origin". This article is incorporated herein in full by specific reference.

For a single administration of ET-743 at the start of each cycle, we prefer a dose in the range 0.2 to 2 mg/m^2, more preferably 0.4 to 1.5 mg/m^2, most preferably 0.7 to 1.2 mg/m^2. At this stage, our data indicates a Recommended Dose of about 0.9 mg/m^2. Thus a dosage equal or above 0.9 mg/m^2 is preferred. More generally, for other cycles which involve a single administration at intervals of 1 week or more, the amount of ET-743 is ordinarily in the range 0.7 to 1.2 mg/m^2. Lower amounts are suitable where there is repeat dosing on a daily schedule.

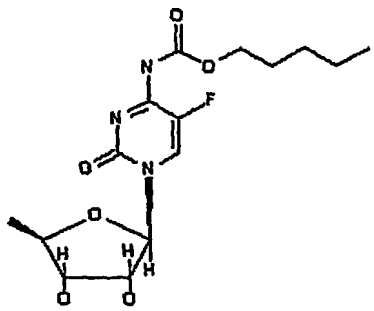
Most preferably, the ET-743 is given by infusion at a dose of about 0.9 mg/m^2- 1.4 mg/m^2, preferably about 0.9 mg/m^2- 1.2 mg/m^2 , most preferably about 0.9 mg/m^2 on day 1 of a 3 week cycle.

As noted in the incorporated article by Kesteren, the combination of ET-743 with dexamethasone gives unexpected advantages. It has a role in hepatic prophylaxis. We therefore prefer to administer dexamethasone to the patient, typically at around the time of infusing the ET-743. For example, we prefer to give dexamethasone on the day before ET-743, and/or the day after ET-743. The administration of dexamethasone can be extended, for example to more than one day following ET-743. In particular, we prefer to give dexamethasone at days –1, 2, 3 and 4 relative to a single administration of ET-743 on day 1 of a cycle.

The ET-743 is administered as part of a combination therapy with a pro-drug of 5-fluorouracil, preferably capecitabine.

Capecitabine is of the formula:

[redacted]



Capecitabine is indicated for the treatment of certain cancers. Information is available on the website www.xeloda.com, and the extensive scientific literature on capecitabine. Capecitabine is a pro-drug which is readily absorbed from the gastrointestinal tract. In the liver, a 60 kDa carboxylesterase hydrolyzes much of the compound to 5'-deoxy-5-fluorocytidine (5'- DFCR). Cytidine deaminase, an enzyme found in most tissues, including tumors, subsequently converts 5'-DFCR to 5'-deoxy-5-fluorouridine (5'-DFUR). The enzyme thymidine phosphorylase (dThdPase) then hydrolyzes 5'-DFUR to the active drug 5-fluorouracil (5-FU). Many tissues throughout the body express thymidine phosphorylase. Some human carcinomas express this enzyme in higher concentrations than surrounding normal tissues.

The capecitabine is administered orally as part of the cycle of treating the patient. We prefer repeat doses on a daily basis as part of the cycle. We prefer that the capecitabine is given for a majority of the days of the cycle, for example for about 2/3, 3/4 or some other fraction of the cycle. For a cycle of 3 weeks, we prefer administration for 14 days, especially days 2 to 15 of a 3 week cycle. Other administration protocols can be designed having regard to this embodiment. In general, the capecitabine is not given on a day when ET-743 is administered, and

preferably commencement of administration of capecitabine is on a day after ET-743 administration.

In one embodiment the dosage amount of capecitabine is preferably it in the range from 500 to 3000 mg/m^2/day, more preferably 1500 to 2500 mg/m^2/day. At this stage, we currently prefer a dose of 2000 mg/m^2/day. This dosage can be administered in fractions, for example in a twice-daily regimen.

Most preferably, the capecitabine is given orally at a dose of about 2000 mg/m^2/day on days 2 to 15 of each cycle.

Other pro-drugs of 5-fluorouracil can be employed in place of capecitabine. Such pro-drugs include other compounds which metabolize to 5'-deoxy-5-fluorouridine, and thence to 5-fluorouracil. For example, reference is made to US 4,996,891 to Fujiu *et al.*, and US 5,472,949 to Arasaki *et al.* The patents are incorporated herein in full by specific reference. In particular, for the present invention, we prefer that the pro-drug is a compound of claim 1 of US 4,966,891 or a compound of claim 1 of US 5,472,949.

Depending on the type of tumor and the developmental stage of the disease, the treaments of the invention are useful in preventing the risk of developing tumors, in promoting tumor regression, in stopping tumor growth and/or in preventing metastasis. In particular, the method of the invention is suited for human patients, especially those who are relapsing or refractory to previous chemotherapy. First line therapy is also envisaged.

Preferably, the combination therapy is used according to the above schedules and dosages for the treatment of sarcoma, osteosarcoma,

ovarian cancer, breast cancer, melanoma, colorectal cancer, mesothelioma, renal cancer, endometrial cancer and lung cancer. Most preferably the patients are breast cancer patients.

In a further aspect of the present invention, a medical kit for administering ET-743 in combination with a pro-drug of 5-fluorouracil is provided, comprising printed instructions for administering ET-743 according to the dosing schedules set forth above, and a supply of ET-743 in dosage units for at least one cycle, wherein each dosage unit contains the appropriate amount of ET-743 for the treatments as defined above and a pharmaceutically acceptable carrier.

Although guidance for the dosage is given above, the correct dosage of the compound will vary according to the particular formulation, the mode of application, and the particular situs, host and tumor being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

EXAMPLE: Phase I Clinical trial

Objectives

Determine the maximum tolerated dose (MTD) of the combination of ET-743 over 3 hours intravenously on Day 1 and capecitabine orally twice daily on Days 2-15.

Evaluate the safety profile of this regimen.

Estimate the peak plasma ET-743 concentrations at each dose level.

Eligibility Criteria

Standard inclusion criteria, also:

Creatinine and liver function tests within normal limits

ECOG PS 0-1.

Standard exclusion criteria, also:

Known CNS metastasis

Peripheral neuropathy > grade 1.

Dose-Limiting Toxicity

Grade 3-4 non-hematologic toxicity

excluding N/V in the absence of optimal supportive care, grade 3 transaminitis < 7 days, and hand-foot syndrome

Grade 4 neutropenia x 5 days or with fever/sepsis

Treatment delay of more than 21 days

Platelets < 25,000.

Treatment Plan

Drug administration

21-day cycles

3-hour intravenous dosing of ET-743 Day 1 every 3 weeks

Dexamethasone Day -1 through Day 3.

Twice-daily oral dosing of capecitabine Days 2-15 every 3 weeks.

Dose escalation

ET -743: 0.4-1.3 mg/m^2

Capecitabine: 2000 mg/m^2/day, no escalation.

Dose reduction

Dose-limiting toxicity or grade 3-4 hand-foot syndrome

Elevated alkaline phosphatase or total bilirubin, any grade

No more than 2 dose reductions allowed

Data Collection

Pharmacokinetic sampling

Cycles 1 and 2, Day 1: ET -743 10 minutes before EOI

Toxicity assessments.

Weekly and PRN through Cycle 3 Day 1, then Days 1 and 15 each cycle and PRN

Biological sampling :

10 mL blood sample for pharmacogenetic analysis

Response assessments

Repeat baseline imaging studies every 2 cycles and EOS.

Patient Characteristics

Number of patients (courses)	14 (50)
Median courses/patient (range)	2 (1-10)
Male:female	5:9
PS 0:1	3:11
Median age (range)	52 (19-70)

Prior chemotherapy (none)	13 (1)
Tumor types	
sarcoma	7
breast, ovarian, cervical, cholangiocarcinoma, gastric, melanoma, vaginal, adenocarcinoma	1 each

Enrollment

Cohort	ET-743 (mg/m^2)	Capecitabine (mg/m^2)	# Patients	# courses
1	0.4	2000	3	13
2	0.6	2000	6*	23
3	0.75	2000	3	10
4	0.9	2000	2**	4

*DLT: grade 3 mucositis and febrile neutropenia

**DLT: grade 3 nausea and dehydration

Drug-Related Hematologic Toxicity

	Grade/Number of Courses	
	3	4
Neutropenia	2	1
Thrombocytopenia	0	0
Anemia	1	0

(Total courses administered: 50)

Drug-Related Non-Hematologic Toxicity

	Grade/Number of Courses			
	1	2	3	4
Nausea/Vomiting	25/11	0	4/2	0
Fatigue	15	7	1	0
Transaminitis	29	7	0	0
Hand-Foot Syndrome	10	9	2	0
Diarrhea/Constipation	8/13	1/3	4/0	0
Alk Phos/Bilirubin	11/6	1/5	0	0
Mucositis	4	1	1	0

(Total courses administered: 50)

Antitumor Activity

13 of 14 patients are evaluable for response (1 patient removed from study for toxicity after 1 cycle).

Seven patients (4 sarcoma, 1 each gastric, breast, vaginal, adenocarcinoma) have stable disease after 10, 6, 5, 2, 3, 4, and 3 cycles; 1 breast and 2 sarcoma patients continue on study.

One patient with cholangiocarcinoma has a partial response ongoing after 8 cycles.

Five patients progressed after 1- 2 cycles

What is claimed:

1. A method of treating a subject having or at risk for cancer, comprising: administering ecteinasadin-743 (ET-743) to the subject; and administering 5-fluorouracil to the subject, wherein the ET-743 and 5-fluorouracil are administered at a therapeutically effective dose, to thereby treat cancer.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/GB04/050026

International filing date: 15 November 2004 (15.11.2004)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/519,690
Filing date: 13 November 2003 (13.11.2003)

Date of receipt at the International Bureau: 11 April 2005 (11.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse